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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/613,262	GILBOA ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/20/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *1-9,16-18 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-15,19-21 and 23-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the supplemental restriction requirement received on 6/20/07 has been entered. Applicant's election without traverse of the invention of TERT as the tumor antigen is acknowledged. Applicant's previous election without traverse of group VI and the species VEGF was discussed in detail in the previous action, as was examiner's decision to rejoin the inventions of groups V-VIII. The restriction requirement is therefore made final.

Applicant's previous amendment filed on 10/10/06 added new claims 19-35. Claims 1-35 are now pending in the instant application. Of these, claims 1-9, 16-18, and 22 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 10-15, 19-21, and 23-35 are therefore currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 10/10/06 and 7/5/07 have been considered.

Drawings

The objection to the drawings and specifically Figure 4 is withdrawn in view of applicant's submission of a clearer copy of the Figure and further in view of applicant's argument that Figure 4 is in fact a copy Figure and that a petition to accept color drawings has been filed in this application.

Claim Rejections - 35 USC § 102

The rejection of claims 10-12 under 35 U.S.C. 102(b) as being anticipated by WO 99/45018 (September 10, 1999), hereafter referred to as Hicklin et al., is withdrawn in view of applicant's amendments to the claims such that they now recite that a composition comprising antigen presenting cells presenting at least one angiogenesis-related antigen and antigen presenting cells presenting at least one tumor antigen.

The rejection of claims 10-15 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,853,719 (December 29, 1998), hereafter referred to as Nair et al. , as evidenced by Heer et al. (2001), Clin. Can. Res., Vol. 7, 3491-3494, is maintained over claims 10-15 and newly applied to claims 19, 23-25, 29-30, and 32-33. Applicant's amendment adding new claims 19, 23-25, 29-30, and 32-33 necessitated the new grounds of rejection. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The rejection of record is reiterated in view of the newly added claims and the amendments to the previously pending claims.

The applicant now claims a composition for treating cancer comprising antigen presenting cells presenting at least one defined angiogenesis-related antigen and at least one tumor antigen, wherein the angiogenesis related antigen is VEGF, the antigen presenting cells are dendritic cells, and wherein the cells produced by transfecting the cells simultaneously or separately with a nucleic acid preparation comprising mRNA encoding at least one-angiogenesis-related antigen and a separate nucleic acid preparation comprising total tumor mRNA. Regarding the newly added term "defined" in reference to the angiogenesis-related antigen, it is noted that the only recitation of the word "defined" in the specification occurs on page 13, paragraph 59, which recites, ".... targeting two defined and broadly expressed ("universal") antigens...". There is no specific definition of what is meant by "defined". In the interests of compact prosecution, the term "defined" has been interpreted to mean "known".

Nair et al. teaches antigen presenting cells, specifically dendritic cells, transfected with RNA derived from tumors useful for the treatment of cancer (Nair et al., columns 1-3, and 12-14, in particular claim 10). Nair et al. further teaches that the RNA is poly A+ RNA, also known as mRNA, that the RNA derived from the tumor comprises tumor related and tumor specific RNA (Nair et al., columns 1, 3, and 5). In addition, Nair et al. teaches that the RNA is derived from a breast cancer tumor (Nair et al., columns 2, 12, 14, and claim 13). Nair et al. also states that since unfractionated total poly A+ RNA derived from the tumor is used, it is not necessary the specific tumor antigens be identified (Nair et al., column 3, lines 29-32) It is also noted that Nair et al. teaches that tumor specific antigens include RNA present in the tumor cells that is not present in a normal cell, and RNA present at a higher level in a tumor cell than in a normal cell (Nair et al., column 3).

Although Nair et al. does not identify mRNA encoding specific tumor antigens or other antigens present in poly A+ RNA prepared from breast cancer tumor cells, breast cancer tumor cells inherently comprise at least mRNA encoding the tumor antigen CEA and further comprise at least mRNA encoding for the angiogenesis related antigen VEGF. This is evidenced by Heer et al., who teaches that breast cancer cells produce significant amounts of VEGF and further express the tumor antigen CEA (Heer et al., pages 3491 and 3493). Thus, any preparation of poly A+ RNA prepared from a breast cancer tumor cell would comprise mRNA encoding both VEGF and CEA, and a cell prepared using total poly A+ RNA from a breast cancer cell, as taught by Nair et al., would therefore inherently comprises mRNA encoding VEGF and CEA. Note that as VEGF is a known angiogenesis related antigen and that it was further known to be present in breast cancer cells, the presence of VEGF mRNA in breast cancer total mRNA meets the claim limitation of a "defined" angiogenesis related antigen.

Regarding newly added claims 23-25, 29-30, and 32-33, these claims are essentially product by process claims. The claims define the composition based on the method used to make the cells. However, "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). The dendritic cells transfected with total breast tumor mRNA taught by Nair et al. appear to have the identical structure to the cells claimed in claims 23-25, 29-30, and 32-33. Whether the mRNA for the

angiogenesis related antigen and the mRNA for the tumor antigen are present in the same mRNA preparation does not affect the final product which will be a cell comprising mRNA for the angiogenesis related antigen and mRNA for the tumor antigen. The Nair cells comprise just these elements as discussed above. As such, the composition of cells taught by Nair and the compositions of cells claimed appear to be identical in structure though produced by different methods.

The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989).

The applicant argues that Heer et al. states that significant VEGF mRNA is not necessarily inherent to all breast cancer tumors by showing that significant VEGF mRNA was not found in lobular breast carcinoma. In response, Nair teaches the use of total mRNA from breast cancer tumors not limited to lobular breast carcinoma. Heer et al. clearly teaches elevated levels of VEGF in ductal breast cancer, the most predominant form of breast cancer. As such, the teachings of Nair to use total mRNA from breast cancer clearly indicates the use of mRNA from the predominant form of breast cancer, ductal breast cancer. Thus, applicant's argument is not persuasive.

The applicant further argues that Nair does not teach cells such as can be provided by transfection of antigen presenting cells with a defined angiogenesis antigen in addition to tumor derived RNA. In response, please see discussion of product by process in relation to the instant claims above, which concludes that the structure of the Nair et al. dendritic cell composition is identical to that claimed regardless of the differences in the method of making the composition.

Finally, regarding applicant's argument that the specification teaches that synergistic results were obtained from expressing both an angiogenesis related antigen and a tumor antigen in dendritic cells, it is noted that none of the cited examples utilize VEGF, the elected species of angiogenesis antigen, and that as the instant rejection is a rejection for anticipation under 35 U.S.C. 102, not an obviousness rejection under 35 U.S.C. 103, it is enough that the prior art teach the same structure as the claimed composition. "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or *In re Best*, 195 USPQ 430, 433 (CCPA 1997). Therefore, applicant's arguments are not found persuasive.

Applicant's amendments to the claims, including the addition of new claims has necessitated the following new grounds of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-12, 14-15, 19-21, 23-30, and 32-35 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Nair et al. (2000) Nature Medicine, Vol. 6 (8), 1011-1017, in view of WO 99/45018 (September 10, 1999), hereafter referred to as Hicklin et al., and Cheng et al. (2001) J. Clin. Invest., Vol. 108 (5), 669-678.

The claims recite a composition for treating cancer comprising antigen presenting cells presenting at least one defined angiogenesis-related antigen and at least one tumor antigen,

wherein the angiogenesis related antigen is VEGF, the antigen presenting cells are dendritic cells, and at least one tumor antigen is either TERT or a mixture of tumor antigens. The applicant further claims wherein the cells are transfected simultaneously or separately with a nucleic acid preparation encoding at least one-angiogenesis-related antigen and a separate nucleic acid preparation comprising total tumor mRNA or mRNA encoding TERT. Regarding the newly added term "defined" in reference to the angiogenesis-related antigen, it is noted that the only recitation of the word "defined" in the specification occurs on page 13, paragraph 59, which recites, ".... targeting two defined and broadly expressed ("universal") antigens...". There is no specific definition of what is meant by "defined". In the interests of compact prosecution, the term "defined" has been interpreted to mean "known".

Nair et al. teaches dendritic cell vaccines for inducing anti-tumor immunity which comprise dendritic cells transfected with either TERT mRNA or total mRNA from a prostate tumor which expresses TERT (Nair et al, pages 1011, 1013-1015, Figures 3-5). Nair et al. differs from the instant invention by not teaching that the dendritic cells are further transfected with a nucleic acid preparation comprising the angiogenesis-related antigen VEGF.

Hicklin et al. supplements Nair et al. by teaching dendritic cells which have been pulsed with an angiogenesis-related antigen or transfected with DNA encoding an angiogenesis-related antigen, and the use of the cells to treat tumors through inhibition of tumor angiogenesis (Hicklin et al., pages 1, 16-17, and 21-25, especially claims 1-2, 17-18, and 23). Specifically, Hicklin teaches antigen presenting cells that are dendritic cells, and an angiogenesis related antigen that is VEGF (Hicklin et al., pages 17 and 21, and page 8).

While neither Nair et al. nor Hicklin et al. specifically suggest combining the strategies of inhibiting angiogenesis and immunizing against a tumor antigen to treat cancer, it was common in the state of the art of tumor therapy at the time of filing to combine different therapeutic modalities in the treatment of cancer. Further, Cheng et al. specifically provides motivation for combining an antigen-specific cancer immunotherapy with an antiangiogenesis therapy. Cheng et al. teaches, " The ideal cancer treatment should be able to eradicate systemic tumors at multiple sites in the body while having the specificity to discriminate between neoplastic and nonneoplastic cells. In this regard, antigen-specific cancer immunotherapy and antiangiogenesis represent two attractive approaches for cancer treatment. Activation of antigen-specific T cell-mediated immune responses allows for killing of tumors associated with a specific antigen while inhibition of angiogenesis controls neoplastic growth by sequestering neoplastic cells form an adequate blood supply. Therefore an innovative approach that combines both mechanisms will likely generate the most potent antitumor effect.:" (Cheng et al., page 669). Thus, based on the motivation to combine antigen specific immunotherapy and anti-angiogenesis provided by Cheng et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to combine the dendritic cell vaccines transfected with TERT mRNA or total tumor mRNA comprising TERT mRNA taught by Nair et al. with the dendritic cells transfected with DNA encoding VEGF taught by Hicklin et al., or alternatively to transfect the TERT mRNA dendritic cells of Nair et al. with the DNA encoding VEGF taught by Hicklin et al.. Further, based on the high level of skill in the art of molecular biology and in transfecting dendritic cells as evidenced by Nair et al. and Hicklin et al., the skilled artisan would have had a reasonable expectation of

success in making a composition comprising dendritic cells transfected with TERT mRNA or total tumor mRNA and a nucleic acid encoding VEGF.

Claims 13 and 31 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Nair et al. (2000) Nature Medicine, Vol. 6 (8), 1011-1017, in view of WO 99/45018 (September 10, 1999), hereafter referred to as Hicklin et al., and Cheng et al. (2001) J. Clin. Invest., Vol. 108 (5), 669-678, as applied to claims 10-12, 14-15, 19-21, 23-30, and 32-35 above, and further in view of Nair and Boczkowski et al. (2002) Exper. Rev. Vaccines, Vol. 1 (4), 507-513.

The applicant claims antigen presenting cells transfected with mRNA encoding TERT and mRNA encoding VEGF.

The teachings and motivation provided by Nair et al., Hicklin et al., and Cheng et al. to make dendritic cells transfected with TERT mRNA or total tumor mRNA, and DNA encoding VEGF are presented in detail above.

However, while Hicklin et al. teaches the transfection of dendritic cells with DNA encoding VEGF, Hicklin et al. does not teach or suggest transfecting the dendritic cells with mRNA encoding VEGF. Nair and Boczkowski supplement the teachings of Hicklin et al. by providing motivation for using mRNA transfection over DNA transfection of dendritic cells. Nair and Boczkowski teach that the use of DNA to transfect dendritic cells presents some problems that can be avoided by the use RNA, such as need to get DNA into the nucleus for transcription, the potential DNA integration into the host cell genome, and non-specific immune stimulation caused by the DNA (Nair and Boczkowski, page 508, column 2). Therefore, based on the advantages of RNA transfection of dendritic cells over DNA transfection provided by

Nair and Boczkowski, it would have been *prima facie* obvious to the skilled artisan to substitute VEGF mRNA transfection for DNA transfection to make dendritic cells expressing VEGF. Further, based on the high level of skill in the art of molecular biology and transfecting dendritic cells with mRNA as shown by both Nair et al. and Nair and Boczkowski, the skilled artisan would have had a reasonable expectation of success in making a dendritic cells transfected with TERT mRNA and VEGF mRNA.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 26 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 recites that the antigen presenting cells have been transfected so as to express "isolated" tumor antigen. The use of the word "isolated" in the context of the claim is confusing since the claim is drawn to a composition comprising antigen presenting cells transfected with at least two nucleic acids encoding an angiogenesis related antigen and a tumor antigen. It is unclear how the antigen presenting cell can express an "isolated" antigen since the word isolated refers to removal of the antigen from other material and the composition clearly comprises numerous components. Further, as a composition claim, the claim does not contain any step

where the expressed antigen is "isolated" from any of the other constituents in the composition. Therefore, the metes and bounds of the claim cannot be determined.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300.** Please note that all official communications and responses sent by fax must be directed to the technology

center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633